

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

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VRC Launches Clinical Trials MODIFIED VACCINIA TARGETED AS POTENTIAL SMALLPOX VACCINE

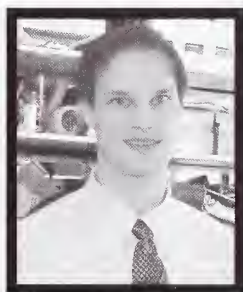
by Fran Pollner

A clinical trial begun in the waning days of 2002 may yield results by late summer that will offer up a safer smallpox vaccine than the currently available Dryvax formulation.

In late December, as the Bush administration launched its smallpox vaccine plan with mandatory inoculation of military personnel, the Vaccine Research Center launched its first human trial to determine whether modified vaccinia Ankara (MVA) can confer equal protection against smallpox without the adverse effects that have made Dryvax so controversial.

Results will not be forthcoming in time to alter vaccine choice for the military and the first waves of health-care workers scheduled for smallpox vaccination under the Bush plan. But much more will be known about the safety and immunogenicity of MVA by the time of voluntary vaccination of the general public—currently scheduled to begin in 2004, Lewis McCurdy, principal investigator in the VRC trial, noted in an interview with the *Catalyst* during the first week of enrollment.

The trial involves vaccine-naïve persons between 18 and 30 years old; the VRC is also planning to launch another study early this year that will test MVA in people age 31 to 60 with



Lewis McCurdy

ELIAS ZERHOUNI: LIVING IN INTERESTING TIMES

by Fran Pollner and Celia Hooper

Sixteen-hour workdays have been the norm for Elias Zerhouni since he relocated last May from the Johns Hopkins University School of Medicine to Building 1 on the NIH Bethesda campus. "I have never worked harder in my life," he told *The NIH Catalyst* in an interview in early December, a little more than six months into his incumbency as NIH director.

Zerhouni arrived at NIH at a time when the institutes were riddled with vacancies and the national and international significance of biomedical research had become even more prominent against the backdrop of potential bioterrorism.

Since his arrival, he has appointed two new institute directors—Thomas Insel at NIMH and Ting-Kai Li at NIAAA—and he says that additional announcements are imminent. He has also become nearly as familiar with the halls of Congress and the offices of the executive as with the lecture halls and labs of NIH.

Q: How's the job so far? Any surprises?

ZERHOUNI: It's pretty good.

It's working 16 hours a day, every day, but in looking at the past six to seven months that I've been here, I'm amazed at how much has been accomplished: We've had intense brainstorming sessions and a retreat with the directors; we've outlined priorities and initiatives for NIH research; we've recruited new directors.

As for surprises, the biggest surprise is the complexity of it. There are so many constituencies, and the job is very public—before, I had to scream to be heard; now anything I whisper becomes big news. You have to readjust.

But it's the complexity of the inputs—inputs from the institutes, the scientific community, the Congress, the public—



Fran Pollner

Elias Zerhouni

this job requires more breadth than I had expected. And the need for communications is much greater across the board than I had expected. I've learned a lot in talking to many of the constituencies.

Q: What seem to be the chief concerns of the constituencies?

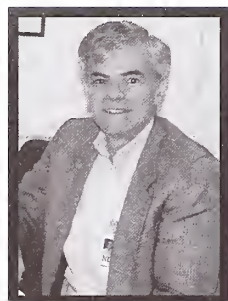
ZERHOUNI: Everyone wants to be re-

continued on page 4

CONTENTS

1 Elias Zerhouni: Living in Interesting Times	8-10 Building Blocks: Building 50 Revisited
VRC Seeking Safer Smallpox Vaccine	11-13 Recently Tenured
2 From the DDIR: The Postdoctoral Experience at NIH	14 Demystifying Medicine/ Performance Contracts
3 Training Grounds Near and Far	15 Cartoon For the New Year
	16 The Last Question

THE POSTDOCTORAL EXPERIENCE AT NIH: SOME NEW IDEAS



Michael Gottesman

"...one aspect of the intramural program deserves special mention and emphasis. It is as a training ground for young investigators . . . that the institution has achieved its most singular influence on the progress of American science."

—Lewis Thomas

(*"NIH: An Account of Research in Its Laboratories and Clinics,"* DeWitt Stetten, Jr., Editor; Foreword, p. xviii, Academic Press, 1984)

There are 3,200 postdoctoral fellows at NIH, reflecting our enormous and long-standing commitment to, and responsibility for, training the next generation of biomedical researchers. In this column, I have frequently written about the imperative to provide appropriate mentoring and training experiences for our fellows and have tried to use this bully pulpit to stimulate the formulation of guidelines and guides to codify high standards for training at NIH.

As a result of the efforts of the Scientific Conduct and Ethics committee at NIH, chaired by Joan Schwartz, assistant director, Office of Intramural Research; the NIH Fellows Committee (FELCOM); and the Scientific Directors, several documents have been created and revised to reflect the high, evolving standards we have set for ourselves in postdoctoral training and mentoring.

The "Guide to Training and Mentoring in the Intramural Program" * provides an outline of our goals and expectations for both mentor and trainee. This has recently been supplemented by three appendices created by the Scientific Directors, reflecting advice derived from a mentoring survey developed by FELCOM.

As requested by the fellows, these documents provide specific guidelines for the mentor and for the trainee, along with a list of topics the mentor and trainees should discuss as part of the annual evaluation of each postdoctoral fellow. We have asked the institutes to follow these guidelines within all parts of the intramural program, with annual evaluations beginning this year.

We should not stop with the use of these documents. The next step is to acknowledge that postdoctoral training is the last major component of a continuum of academic training whose success is measured by how well our fellows are prepared for a career in biomedicine. This future will require expertise in subject areas that not all our fellows had the opportunity to acquire in graduate

school. Training should reflect the need to develop a multidisciplinary workforce, to make optimal use of the special resources at NIH, and to respond appropriately to the skills and talents of our individual fellows.

At the same time, recent trends indicate that the age at which scientists become independent is increasing, and this extended training should not unnecessarily delay the start of independent careers.

Thus, I propose that in addition to the excellent laboratory and clinical research opportunities currently available to our fellows, we develop a more formal postdoctoral training program with the following characteristics:

- Availability to all postdoctoral fellows of coursework in subject areas such as bioinformatics, genomics, integrative biology, and translational research

- Cross-training in multiple disciplines, perhaps through co-mentoring arrangements (the new joint NIH-NIST fellowship in biology and physical sciences is a pilot example of such interdisciplinary training)

- Development of requirements for a certificate-of-training in the intramural program, reflecting areas of greatest scientific strength at NIH

- Improved career counseling and specific guidance and coursework to help fellows achieve their career goals

- Discussion and development of milestones for postdoctoral training to facilitate achievement of goals within a reasonable period of time.

I hope these ideas will be widely discussed among our principal investigators and fellows. I have assembled a group of scientists and educators to develop specific implementation plans for consideration by the Board of Scientific Directors and other senior NIH leaders. The goal is to develop new concepts for postdoctoral training in biomedicine and to make the postdoctoral experience in the NIH intramural program even more attractive and effective. ■

—Michael Gottesman
Deputy Director for Intramural Research

* see <http://www1.od.nih.gov/oir/sourcebook/ethic-conduct/TrainingMentoringGuide_7.3.02.pdf>

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TRANSATLANTIC D.PHIL. PARTNERSHIP

by Valerie McCaffrey, OE

Two doctoral programs that partner NIH with either Oxford or Cambridge University in the United Kingdom are entering their second full year. The NIH-Oxford University Scholars in Biomedical Research Program and the NIH-Cambridge University Health Sciences Research Scholars Program offer students Intramural Research Training Awards to earn a D.Phil. degree in biomedical and health research.

Award recipients participate in an interdisciplinary training program and a collaborative research project under the joint mentorship of intramural faculty of two institutions: the NIH and either Oxford or Cambridge University. Participants spend time in laboratories at each institution as they progress towards their degrees.

The projects of last year's inaugural class spanned a range of disciplines that included neurobiology, genetics, structural biology, molecular biology, immunology, cancer biology, and clinical sciences.

To Be a Mentor

Intramural investigators in all institutes are eligible to collaborate in the training of a scholar (including those who are not stationed at the Bethesda campus). To serve as a mentor, the investigator must be at the rank of tenure-track or above and supervising an independent research program.

The first step is to create a proposal for a collaborative research project suitable for a doctoral student. This is done in conjunction with eligible investigators at Oxford or Cambridge. The next step is to send a one-paragraph description of the collaborative project(s), with links to the web pages and/or e-mail addresses of mentor and overseas collaborators, to Andre Nussenzweig at <nussenza@exchange.nih.gov>.

These investigator-initiated projects will then be advertised to scholars, who are encouraged to discuss them directly with the PIs. It is also possible for a scholar to create a course of study with a particular mentor in mind and initiate contact with that person.



Cambridge

To Be a Scholar

To be eligible for this program, a student must be a U.S. citizen or permanent resident with a bachelor's degree from an accredited U.S. college or university. All applicants are expected to have had undergraduate preparation in biology, chemistry (both inorganic and organic), physics, and mathematics. Candidates should demonstrate outstanding academic performance and promise for a career in biomedical



Oxford

research. Previous laboratory research experience is also a strong qualification for this program. Students already enrolled in medical schools, as well as college graduates interested in pursuing a D.Phil., are encouraged to apply.

There is also an Advanced Scholar track for second- or third-year graduate students in the biomedical sciences at Oxford or Cambridge that supports them for additional years of graduate work to carry out research in an intramural laboratory at NIH.

For more information on the Advanced Scholar track or for other questions relating to the Oxford and Cambridge programs, contact coordinator Michael Lenardo at

<lenardo@nih.gov>.

More information on these and other doctoral programs can be found on the Graduate Partnerships Programs web page at

<<http://gpp.nih.gov>>.

Last Call

To put your two creative cents into a new look for the back page of the *Catalyst*, see the **last** question on the back page.

Also, for anyone with an outdated bookmark, the *Catalyst* website is <<http://www.nih.gov/catalyst>>.

CROSS-COUNTRY TRAINING

Applications for the 2003-2004 NIH-Duke Training Program in Clinical Research and the University of Pittsburgh Training in Clinical Research Program are available in Building 10, Room B1L403. The deadline for applying is **March 1, 2003**.

NIH-Duke

The NIH-Duke collaboration, implemented in 1998, is designed primarily for physicians and dentists who desire formal training in the quantitative and methodological principles of clinical research. Offered via videoconference at the Clinical Center, the program allows the integration of a student's academic coursework with his or her clinical training.

Academic credit for the program may be applied toward satisfying the degree requirement for a Master of Health Sciences in Clinical Research from Duke University School of Medicine in Durham, N.C.

Applicants who have been accepted into the program will be notified by July 1, 2003. For additional information regarding course work and tuition costs, please refer to the program website at

<<http://tpcr.mc.duke.edu/>>.

E-mail queries may be addressed to

<tpcr@mc.duke.edu>.

Pittsburgh

The University of Pittsburgh Training in Clinical Research Program is designed for Ph.D.s and allied health professionals (such as pharmacists and nurses) to gain the knowledge and skills required to conduct clinical investigation, as well as more extensive knowledge of a specific area of concentration. Physicians and dentists are also eligible for this program.

Participants can opt to receive a Certificate in Clinical Research (15 credits) or a Master of Science in Clinical Research (30 credits) from the University of Pittsburgh.

For more information, visit the program website at

<http://www.cc.nih.gov/cc/cc_pitt/index.html>

or e-mail <tcp@imap.pitt.edu>. Successful applicants will be notified by May 29, 2003. Enrollment in both these programs is limited. Prospective participants should consult with their institute or center regarding the official training nomination procedure. ■

ELIAS ZERHOUNI
continued from page 1



Fran Pollner

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assured that NIH has its act together. The chief concern is that now that we've doubled the NIH budget, is the NIH being true to its mission, is it delivering to the American people? I've been asked why the number of grants has not doubled, whether the new buildings are really necessary.

Any high-profile federal agency that receives significant dollars will be questioned about whether those dollars are well used—and some people will think they are and some will not.

Q: Will our construction plans present a political problem?

ZERHOUNI: No, I don't think so.

Q: What's your assessment of the intramural research program?

ZERHOUNI: The intramural program is the most impressive biomedical research program in the world by virtue of its size, complexity, and the breadth of its endeavors.

What's really important to me is that the research conducted by the intramural program—because it is not subject to renewed competitive peer review—has to be second to none and should fulfill a unique mission. It should do those things that are truly inaccessible to extramural institutions, things the nation needs done that neither industry nor academia can do. A good example is

vaccine research. Intramural research should break new ground. The Clinical Center should define itself as the only place in the country where truly groundbreaking clinical research can be done.

Q: Do you think NIH research lives up to these criteria?

ZERHOUNI: So far, from what I can tell, there's quite a bit of outstanding work being done in the intramural program. I don't know enough yet of all the details to say that *every* part of the program is groundbreaking, that everything has been looked at by the intramural community in terms of its being innovative, creative, and risk taking. We have not yet done a formal, across-the-board analysis—that first level of analysis—to define unique research opportunities or major roadblocks that cannot be addressed elsewhere.

I am impressed by the scientific directors, by their commitment to innovation. Their collegiality and core values and spirit—an NIH spirit—are very strong, and they are committed to sustaining the worldwide leadership of the intramural program as research paradigms change. NIH has a major role to play in advancing methodologies for research—discoveries in structural biology; the study of molecular complexes, which no one really knows how to do; the study of membrane-bound proteins—all the issues that relate to what I call mathematical biology.

Q: Is the national focus on bioterror-related research relegating other NIH research to places of lesser importance and funding? How does the creation of the Department of Homeland Security affect NIH research?

ZERHOUNI: One of the very first things on my agenda after I got here was this issue. Initially, it was presented that NIAID's biodefense research program would go into homeland security, and we worked very hard over several months regarding this issue. During talks involving the administration, the Depart-

ment [of Health and Human Services], [NIAID director] Tony Fauci, and myself, we made clear that we could not recreate all the scientific skill set established in NIAID and in the extramural community, and that the country was well served by what we'd created. There will be a need to coordinate and consult with the Department of Homeland Security—that's what NIH is all about—but I am not aware of any movement of people or shifts in research resources.

As for the effect of funding on other NIH research, we've been given extra resources for biodefense research, so there should be no effect.



Fran Pollner

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Q: With the advent of the current administration, there has been an emphasis on "one HHS." Do you think NIH has sufficient autonomy from the Department? Is there micro-management of NIH operating procedures or censorship of NIH's scientific voice?

ZERHOUNI: "One HHS" is the secretary's strategy for coherence in health research policy and for the coordination that has been lacking in utility functions, such as e-mail systems and software for results reporting. "One HHS" is not a power play but a collaborative process so that services and functions can be shared throughout the Department. It's an effort to use taxpayer

money efficiently, to be accountable and transparent.

Decentralization is good for a knowledge enterprise like NIH. You cannot do research the same way you process bills, but we can have common approaches to common problems when it comes to utility functions. NIH is not a paradigm of efficient management. For instance, we could not report clinical research consistently across NIH—there was no consistent set of numbers to report to Congress because there weren't common measures of clinical research

activities among the institutes.

Regarding scientific censorship, or "one scientific voice," I have not seen any censorship. I personally speak freely and will continue to, and that's reflected in my public statements and testimony to Congress.

Sometimes it is necessary to present a central scientific voice in scientific com-



Fran Pollner

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UNICATIONS: Take the example of the Women's Health Initiative and the forum we held here [see *The NIH Catalyst*, November-December 2002, page 1]—would it have been better to have NCI, NHLBI, and OD all do their own things? Or was coordination beneficial?

With respect to personal views, indi-

Roadblocks, Road Maps, and 'The Perfect Storm'

Immediately after talking to *The NIH Catalyst*, NIH Director Elias Zerhouni sat down with the heads of NIH's Boards of Scientific Counselors (BSC)—the outside panels that critically review NIH intramural investigators every four years.

Offering "the bad news" first, Zerhouni opened with his apprehensions about NIH funding and likened the fiscal environment to "a 'Perfect Storm' scenario." Ominous converging forces include the U.S. government's going from fiscal surpluses to deficits, a teetering economy, support for a new Department of Homeland Security, other post-9/11 security measures, the war on terrorism, and the possibility of war in Iraq—all transpiring at the moment NIH was to receive the final installment of its promised five-year budget doubling.

With NIH operating under a continuing resolution at least into January, Zerhouni said it was not clear when and at what levels NIH's 2003 budget would be approved. A self-avowed optimist, however, he said President Bush was committed to the need for doubling NIH's budget. "At the end of the day, it will go forward. We should do well, but it is not that predictable." He observed that there are probably thicker clouds gathering over the 2004 budget, the year NIH was to attempt a "soft landing" after the years of increase.

At the BSC meeting, Michael Gottesman, deputy director for intramural research, clarified that a doubling of the NIH budget has not and will not mean a doubling of the intramural research budget. Although there has been an increase in dollars going to intramural research, overall the intramural program has declined as a percentage of the NIH budget from 11.2 percent in 1993 to 9.6 percent in 2002.

On a brighter note, Zerhouni told the BSC chairs about his efforts to identify key roadblocks to the advancement of biomedical research and to plot a map that will guide research to achieve the progress that taxpayers and legislators expect after doubling NIH's budget. Zerhouni said that he had brought to NIH more than 100 scientists to help him over the summer with his quest for a road map. He made a more formal presentation of the roadblocks and road maps when he met with his Advisory Committee to Director (ACD) on December 5.

Citing dramatic changes in the biomedical research enterprise, the experts stressed the overwhelming amounts of data that are emerging—much of it poorly understood. With extraordinary technology driving the process, some individual laboratories are now churning out results that in their complexity, scope, and scale could match what an entire institute

might have produced 10 or 20 years ago. Often the data are within NIH's purview but cross traditional institute lines. High-risk, longer-term studies with potentially large payoffs present the greatest challenges.

Key areas where NIH has a role are in the development of revolutionary technology and novel methods of research, including robotics, nanotechnology, DNA array technology refinement, reagents, 3-D protein structures, models of protein-protein interactions, molecular libraries (going beyond cDNA databases) that can be interrogated, and bioinformatics methods for resolving the fog of data emanating from labs across the country.

"The scale-up of data generation has been intense," Zerhouni said, "but we have not developed the ability to resolve the data on a temporal or spatial level sufficient to make models, such as of membrane-bound proteins, for example." Speaking to the ACD, Zerhouni pointed out that membrane proteins may account for 30 percent of all biologically relevant molecules.

NIH, Zerhouni said, is being called on to develop these technologies and then make them available to biomedical researchers. Also needed from NIH is a "pathways" view of research that avoids traditional reductionist views and encourages a multidisciplinary approach to explore entirely new avenues of investigation. At the ACD meeting, he emphasized the need to assemble teams of scientists who have cross-trained at least enough to talk to one another about common problems and approaches. He cited five ubiquitous concepts that stand out as areas for discovery: genomics and proteomics, cell signaling, apoptosis, cell trafficking, and cell cycle control.

Needs are particularly acute for clinical research, Zerhouni said, where NIH should define unifying standards that would allow data to be readily extracted, recombined, exchanged, and probed in creative ways. Currently, multiple medical dictionaries and definitions of diseases prevent correlations between different studies, greatly restricting their power. Even the largest individual studies, such as the Women's Health Initiative (see "Disparate Voices Reflect on WHI Data," *The NIH Catalyst*, November-December 2002, page 1) cannot possibly answer all the questions in and of themselves. NIH is the only entity that can step into such areas, Zerhouni said. "We have a role to play."

—Celia Hooper

vidual free speech and academic freedom are essential to a knowledge institution—and I stepped in to defend a scientist at NIEHS who felt his freedoms had been restricted. But one must be careful to present a personal view as just that and not pretend to be representing NIH or use the NIH title to promote one's personal views.

Q: What about embryonic stem cell research?

ZERHOUNI: Let's face it, before the president announced his policy, not one dime of the federal dollar was going into this research. It's a golden opportunity for NIH leadership—as a training ground, as a resource center, as a setter of strategic priorities.

Any new science needs nurturing, and I immediately created a stem cell task force when I got here. We need to not get bogged down in rhetoric but to get down to work. There's a lot we don't know and must know before we can entertain approaches to regenerative medicine.

NIH needs to frame the issue in a factual way. And, really, NIH is the one institution in this country that can serve as the source of trusted information for the public of what is and is not fact, what is speculation and what is real—unfettered by political consideration—in this and all scientific research areas. If you've lost the public trust, you've lost everything. And that's also one reason why you can't have 10 sources of conflicting information.

I came to this job with one very simple view, and that is that disease knows no politics—and I try to make sure that all parties understand that, all sides of the debate understand that. And I have to say that I am impressed by the thoughtfulness of the House and Senate leadership and the high quality of the Congressional staff; the same is true within the administration.

By and large, I have not found the task of sending messages to the political constituencies to be daunting—so long as I have my facts. But the importance of that task is much more than I considered initially. It is a primary priority to be able to interact, educate, coordinate, and strategize to achieve continued understanding by all political parties.

NIH has a tough mission. In the entire scientific spectrum, it is the life sci-

ences that are the grand challenge for now and the foreseeable future. We need to make discoveries at a more rapid pace because time is of the essence when you consider the aging of the population, the growth of our health expenditures, and the new threats that are emerging. We need to accelerate our knowledge base in the life sciences. That is the perspective I try to bring to the political constituencies.

Q: In the scheme of things in apportioning your time as NIH director, do you miss doing clinical radiology?

ZERHOUNI: Not really. I do like to consult on the tough cases—that's what I did before—but right now I'm so totally focused on my job. My philosophy is that it's better to spend 100 percent of your time on your priority early on than 10 percent each on 10 different things because at the end of the day you will not have accomplished anything. But I do want to get back to some imaging research at some point.

Q: Will you do that here?

ZERHOUNI: I hope so. I still have some ideas left.

Q: What are they?

ZERHOUNI: Well, my primary research has been on using quantitative approaches—mathematics, computation—to enhance the basic process of image acquisition to better diagnose and treat disease. Now, of course, quantitative analysis is the standard method, but let me tell you that my early papers—on measuring the intrinsic absorption of X-rays in lesions, on different calcium concentrations in tumors—generated years of controversy.

One submitted paper generated 26 different criticisms needing to be addressed before it could be published. People thought it was too expensive, and there was inherent opposition to the idea of not operating surgically, even though two-thirds of the operations were for benign lesions. (In my experience, any really groundbreaking paper had diffi-



Fran Pollner

I still have some ideas left . . . image-guided microsurgery . . . disease preemption . . .

culty being accepted, while the mundane sailed through.)

We need another quantum jump of imaging in medicine. I envision that in 30 to 40 years there will be no open surgery. Traditional surgery will disappear, as will traditional anesthesia, and there will be only image-guided microsurgery. We're headed in that direction now.

Disease preemption is another research area that I'm hoping to do work in. It involves image guidance and the interaction of energy and biological molecules to put specific cell populations at rest and prevent them from becoming malignant. Breast cancer, for example, arises from less than 1 percent of mammary cells. Why could we not, around the time of menopause, put cells in a quiescent state to prevent the genetic cascade of events that result in breast cancer? Even moderate success would change the incidence of disease.

The concept of preemption has not been explored, and, obviously, this approach has wider applications. This is what I'm hoping to do. ■

SMALLPOX VACCINE TRIAL

continued from page 1

a history of vaccinia vaccination. Assuming successful outcomes, it's anticipated that other studies—not necessarily in the VRC—will be done to determine safety and immunogenicity in more vulnerable populations, such as the elderly, children and infants, and people with skin conditions and other immunocompromised patients for whom Dryvax is contraindicated, McCurdy said.

MVA was originally envisioned by Barney Graham, chief of the VRC Clinical Trials Core, as a potential substitute for Dryvax in the routine vaccination of lab personnel working with vaccinia. The idea to test MVA as a potential new vaccine for smallpox arose with the "threat of bioterrorism after September 11," McCurdy recounted.

Safety First

There's ample reason to believe that MVA's safety will be established in this phase 1/phase 2 trial, McCurdy said. Whereas Dryvax is a vaccinia strain capable of replicating at the lesion site, MVA is an attenuated strain that has been passaged more than 500 times and is unable to replicate in mammalian cells, he noted. He cited clinical studies conducted in Germany in the 1970s demonstrating that the modified strain protected against Dryvax complications and was well tolerated by all recipients, including the elderly and children. Studies of high-dose MVA in immunocompromised macaques, undertaken by NIAID's Bernie Moss and Linda Wyatt in collaboration with Dutch investigators (K.J. Stittelaar, T. Kuiken, R.L. de Swart, et al. *Vaccine* 19:3700-3709, 2001) established MVA's safety in a vulnerable nonhuman primate population. MVA, he observed, is being considered as an HIV vaccine vector.

"MVA should be safe in almost all populations," McCurdy said, "but it's never been field tested against smallpox, and no one knows if it's going to be effective."

Correlates of Immunity

"No one really knows what the correlates of immunity are," McCurdy continued. "After Edward Jenner demonstrated protection using a poxvirus in the late 1700s, people simply continued to use it without understanding why it worked. It's now presumed that the development of neutralizing antibodies is important for protection against smallpox, but this has not been demonstrated specifically."

Because MVA does not cause a visible reaction, or a "take," at the injection site, that cannot be used as a sign of immunity. The VRC investigators will instead be looking for neutralizing antibodies and assessing T-cell function via intracellular cytokine staining for interferon- γ and TNF- α .

To determine whether neutralizing antibodies against vaccinia correlate with neutralizing antibodies against variola (smallpox), which also has never been shown, selected samples will be sent to the Centers for Disease Control and Prevention (CDC), which has the requisite BSL4 laboratory for the study. That work will be done by Inger Damon, who heads the CDC poxvirus section, in collaboration with Graham. The VRC team is also conducting mouse studies to get correlative data on poxvirus protection, which will supplement its clinical findings in the process of pursuing a license for a new vaccine.

"Our hope is that MVA alone will elicit immunity similar to that with Dryvax. If it turns out that MVA alone is not as immunogenic as we think it will be, then it might be worth considering using it several weeks to a month before giving Dryvax to minimize Dryvax complications," McCurdy commented.

The VRC is recruiting 105 people for the study with a vaccine-naïve population. At the time of the *Catalyst* inter-



Fran Pollner

Lewis McCurdy

view, the team had gotten about 60 calls from potential volunteers, most at NIH; 15 people had been screened, and 14 of these qualified for entry. The trial is seeking accrual as quickly as possible, with plans to vaccinate 10 to 20 people weekly. The randomized, blinded trial will pit placebo against each of three MVA regimens: one

dose (1×10^8 pfu); two doses, separated by one month; or three doses at 0, 1, and 3 months. In addition, there will be another cohort in the first group who will receive Dryvax instead of MVA. Three months after their last injection, all volunteers will get a Dryvax challenge. For more on the trial, see

<http://clinicalstudies.info.nih.gov/detail/A_2002-1-0316.html>.

The trial of previously immunized individuals between ages 31 and 60 will get underway in February. To be eligible, candidates must have received their last vaccinia shot at least 10 years ago and have a demonstrable scar. The format will be similar to the first trial, with cohorts receiving either one or two MVA doses followed by a Dryvax challenge. Most of the 80 volunteers needed are expected to come from NIH. For more information, call Tiffany Alley at the VRC, 301-594-8569, or call 1-866-833-LIFE. ■

Computational Approaches to Biological Systems

Advances in computer technology are providing scientists with the quantitative means to analyze, model, and simulate complex biological processes. NIGMS is presenting the following seminar series, featuring scientists on the cutting edge of computational approaches to biological systems:

■ **February 27:** Albert-László Barabási, University of Notre Dame, "Hierarchical network structure of protein-protein and metabolic interactions"

■ **March 27:** Bernhard Palsson, University of California, San Diego, "Bringing genomes to life: The use of genome scale in silico models"

■ **May 29:** Richard Young and David Gifford, Massachusetts Institute of Technology, "Regulation of genome expression in living cells"

■ **June 5:** Leslie Loew, University of Connecticut Health Center, "The virtual cell project"

All seminars will be held in Building 10, in the Lipsett Auditorium from 11:00 a.m. to noon. For information and accommodations, call Kevin Lauderdale at 301-451-6446. ■

BUILDING BLOCKS: ANOTHER LOOK AT THE STOKES BUILDING

Spurred by murmurs of discontent and apocryphal tales of bats in the belfry of the Stokes Building 50, a small band of roving Catalyst reporters talked to about a dozen people working in this award-winning state-of-the-art research facility—the most recently completed new laboratory building on the Bethesda campus. Building 50 was dedicated in June 2001 (see “Looking Nifty at 50,” *The NIH Catalyst*, July–August 2001, page 1) and was fully occupied by the end of that year. It was toward the end of 2002 that we were moved to get the inside story of adjusting to life in Building 50.

The people we spoke with are not a representative sample. In some cases, they were approached because they bailed from the same institute as that particular interviewer. In others, they were asked about their digs in a spur of the moment addendum to a photo-taking session for the Catalyst. Those on the lower floors arrived earlier, when there were more wrinkles, and respondents varied in their attachment to former lab space.

Opinions diverged regarding the wisdom of allocating a lot of space to common areas, but people tended to find such space wasteful rather than conducive to fostering collegial exchanges. There was a “disconnect between what the architect envisioned and what the scientists needed,” said one commenter. Most people felt there were too many locks on doors and corridors that separate each floor’s laboratory “neighborhoods” from one another. They observed that this building feature defeated one of the objectives of the building’s design—to create openness and foster collaboration. Criticisms of the plumbing, water, and artificial lighting were common. And just about everyone mentioned how nice it would be to have food service—or just coffee service—in the building.

Today, Building 50 is abuzz with research, of course, and its window light is often brightened by glistening snow this particular winter. The glitches in the move from drawing board to occupancy of the building were a catalyst for setting new policies to effect smoother transitions from old to new laboratory quarters (see “Moving On: New Policy Formulated,” page 10).



Building 50 Inside

and Out

Masashi Rotte

WATER, WATER EVERYWHERE, BUT . . .

Moving into Building 50 was done “just in time”: As soon as their particular spaces were ready, individual labs moved in regardless of what remained to be done elsewhere.

Rodney Levine, chief of the section on protein function in disease, NHLBI, thus moved into his second-floor quarters amid ongoing construction. His and other labs in the completed areas, he says, suffered damage to equipment and experimental samples when work on the upper floors caused water leaks and electrical outages.

Then there were also the lab benches and electrical wiring that didn’t conform to specifications; the Venetian blinds that were not adjustable; the insufficient lighting; and the crack in the building’s foundation near the shared animal facility.

Tom Kindt, director of intramural research, NIAID, did not move into his fifth-floor lab space until after construction was complete in the fall of 2001—but he still experienced problems. The workmanship on the roof, he says, left a lot to be desired, especially the leaks that contaminated the water reaching the labs, destroying experiments, rendering water unpotable, and, sometimes, causing floods. Leaking pipes in walls and access areas have caused ongoing water damage across the building, he says, leading one research group to construct a makeshift umbrella to protect a vital piece of equipment.

That said, both Levine and Kindt find the building visually appealing and appreciate the natural light that floods it.

“Aesthetically,” Kindt says, “it’s great.”

He notes, however, that he’d anticipated more openness between neighborhoods when the building was in its planning stages.

As one of the scientists representing the building’s future occupants, Kindt had attended planning meetings with Building 50 project managers on a regular basis. Not all parties got all their wishes, but the group did strive for consensus, he recalls. He observes that it’s difficult to predict the actual usability of a building just from blueprints.

Among the last to move into the building—just before 2001 ended—Alan Sher expresses satisfaction with researcher density in the sixth-floor space he shares with Tom Wynn (see “It’s the Ritz,” page 10).

Head of the immunobiology section in the Laboratory of Parasitic Diseases, NIAID, Sher is particularly impressed by the efficient management and availability of Building 50’s shared resources—like the NIAID-run animal facility.

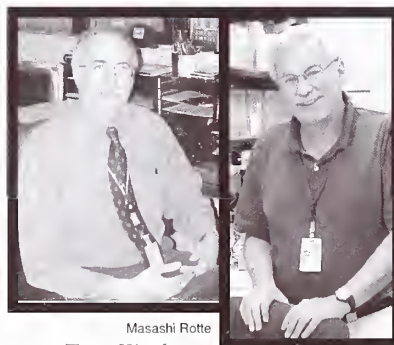
Although many of the building’s occupants point to the locked doors and corridors as thwarting collegiality, Sher says he personally does not feel isolated from other labs and researchers.

For Levine, the ease of interaction among the building’s scientists is critical and a prime topic for discussion by

the scientist steering committee of Building 50, of which he is a member.

The committee, however, has not had sufficient time to address collaboration among labs and scientists, he says, because the meetings have been dominated by the more immediate physical problems that have arisen.

—Masashi Rotte

Masashi Rotte
Tom Kindt

Alan Sher

Who’s on First?

There are directories—some printed and behind glass, some scribbled and taped to the wall—on each floor of Building 50, which provides at least a rough idea of which labs and individuals can be found beyond the locked corridors to the neighborhoods that make up each floor. There are six floors and about 600 scientists in the building.

Floor 1: all occupied by NIAMS

Floor 2: all occupied by NHLBI

Floor 3: shared by NHLBI and NIDDK

Floor 4: a potpourri—shared by NHLBI, NIDCD, NCI, and the NEI and NIDCR directors’ labs

Floor 5: shared by NIAID (including microarray and antibody facilities) and NHGRI

Floor 6: all occupied by NIAID

In the **basement** are a NIAID-managed vivarium, an NMR suite shared by NIDDK and NHLBI investigators, and an electron microscopy suite shared by NIAMS and NCI investigators. ■

PRIVACY ISSUES

The 55 or so members of the NIDDK Laboratory of Cellular and Developmental Biology take up most of the 3rd floor of Building 50 (with the remaining space going to about 35 NHLBI scientists).

Recalling their experiences settling into their new quarters, the administrative staff was more positive about the transition than were the scientists interviewed.

Lab manager and move coordinator Sylvester Jackson has only praise for the assistance of the NIH support service staff who handled the move itself and related chemical and radiation safety issues. Comparing their new quarters to Building 6, whence they came, NIDDK intramural office manager Patricia King says, "We are in such a pleasant building now. Every building should be built like Building 50." They credit the Division of Engineering Services with prompt and able responses to any problems that arose.

But research fellows Holly Davies and Olga Epifano would have preferred that the problems had not arisen in the first place and are not as sanguine about the daily working realities of their lab space. "Even though we have more square footage than before," says Davies, "much of the new space has been used inefficiently." There's less sink space now for the nine people who work in the lab—1.5 sinks instead of three—and because desks and benches are separated, people often must move back and forth to retrieve notebooks and references while doing experiments.

Epifano focuses on the acoustic inadequacies of the workspace. The open design of the benches and desks is aesthetically pleasing, she says, but there's a lack



Rashmi Nemade

Olga Epifano (left) and Holly Davies

of privacy and quiet spaces to work. "It's great to have our own telephones, but when everyone can hear you, the only advantage over a shared phone is that you have your own voicemail," she observes.

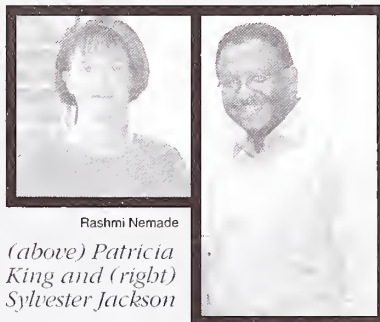
Although the spacious elevator lobbies were designed with the idea of offering more opportunities for researchers to interact and initiate collaborations between institutes, these spaces are rarely used. In fact, Davies and Epifano cannot remember a time when there have been scientists sitting in the lobbies just talking. "It seems this space could have been used for more sinks, benches, desks, and offices," says Davies.

Epifano recalls that in the old building, she would routinely bump into people from other labs and just strike up conversations, but now she has to have a specific reason to go into other lab spaces.

But the most frustrating issues in Building 50, they agree, have been related to the water supply. The water tanks are housed on top of the building where sunlight reacts with microorganisms to contaminate the water—both distilled water and potable water used to wash glassware and hands. "Without a reliable source of water, how can we believe our experimental results?" asks Davies.

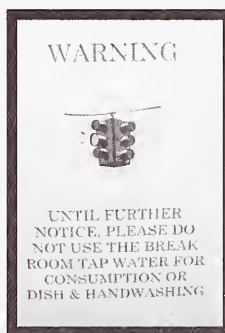
Finally, they wryly observe, the high-tech automatic faucets and automatic toilet flushes in the bathroom are great—when they work.

—Rashmi Nemade



Rashmi Nemade

(above) Patricia King and (right) Sylvester Jackson



Rashmi Nemade

VIBES



Fatima Husain

Xiao-Xia Dong (left) and Mark Ospeck

Kuni Iwasa

NIDCD has an enclave of about 30 scientists on the fourth floor, which, with occupants from no less than six institutes, is the most diverse of Building 50's elevator stops.

Getting from the elevator into NIDCD space, however, notes Gavin Riordan, a lab tech and manager in the section on structural cell biology, is no easy task for individuals without card keys—delivery people, visiting scientists, and temporary interns (who typically "wait forever" for their card keys and have to prop the door open every time they leave the lab).

A telephone at the building's main entrance doesn't help much when a person is at the NIDCD threshold and can't get in or knock loud enough to reach an occupant at the far end of the lab. Doorbells, Riordan suggests, could help.

Within the space itself, a negative quality is the "lack of local humidity control," but the location of the research stations at the center of the building, away from the window light and where there is less vibration—is especially good for electrophysiological experiments, observe Mark Ospeck and Xiao-Xia Dong, postdocs in the lab of Kuni Iwasa.

Iwasa, who heads the biophysics section in the Laboratory of Cellular Biology, is part of the representative assembly of scientists who constitute the Building 50 user group that was created about a year ago to promote scientific exchange among the building's occupants.

Headed by Ed Korn, NHLBI, the group has secured a crosswalk that enables scientists to navigate between Building 50 and other labs more directly without dodging cars.

The committee has been trying to have a coffee stand and tables installed near the entrance to the building so that the ample lobby space can be used to sit around and exchange ideas, as originally intended, Iwasa relates. This effort has so far been unsuccessful.

—Fatima Husain and Fran Pollner

BUILDING 50: AFTER ALL IS SAID AND DONE

It's the Ritz

"I hate to complain because I love this lab," says Tom Wynn, senior investigator in the Laboratory of Parasitic Diseases, NIAID, and head of the immunopathogenesis section. Wynn shares a neighborhood on the sixth floor with Alan Sher, head of the immunobiology section.

"We were one of the last groups in, and the move was smooth. I came from Building 7, one of the oldest on campus—it was like going from Motel 6 to the Ritz. This building has great facilities, well laid-out labs. It's user-friendly—all the desks are by windows and across from the labs.

"The architect, [Frank] Kutlak, did a great job. It's a beautiful building with a great design."

And the complaints? "There's been a chronic problem with water, potable and otherwise. Green sludge. There are breakrooms at the end of each lab block, and we don't drink the water there or wash the cups with it. Now we all drink bottled water."

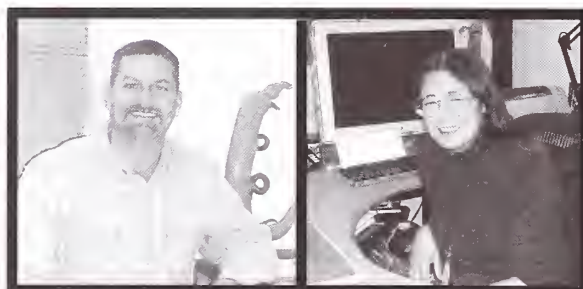
Although he hasn't yet interacted much with investigators from other institutes, Wynn says the multi-institute design should facilitate more exchanges. Noting that NIAID's microarray facility is on the fifth floor, as are the building's NHGRI occupants, he says he plans to do some microarray work with NHGRI scientists.

The building's elaborate card-key access system is good news and bad news. "I have to use mine six different times

to get to my own place some after-hours nights," he says, "but at least I feel safe."

'Every Building Has Problems'

Cecilia Lo, chief of the Laboratory of Developmental Biology, NHLBI, stepped into NIH and the fourth floor of Build-



Tom Wynn (with his worm
Schistosoma mansoni)

Cecilia Lo

ing 50 at the same time. But she knows that her NHLBI colleagues who moved in earlier from Building 6 and onto lower floors of Building 50 had a harder time of it. "They were very unhappy. There were electrical power problems, resulting in samples in the freezer thawing; the cold rooms heated up; there wasn't enough space for all the equipment that had to be relocated."

Her own headaches included "playing Russian roulette" with the quality of the water supply, a problem that was solved by throwing money at it. "We bought apparatus to distill our own water." Lighting problems were also solved by incurring the additional expense of installing suspended fluorescent lights (which took six months) to correct the inadequate indirect lighting that had been selected to illuminate the desk

space. "The desks were by the windows, yes, but no one could see after dark, which is pretty early in winter."

Although Lo deems the "open design and the sun pouring in and the high ceilings" very positive aspects of her space in Building 50, she wishes there were as much openness between neighborhoods as within them.

Lo occupies her neighborhood with Betsy Nabel, NHLBI clinical director and chief of the vascular biology branch. Their labs house about 25 scientists, and they "share equipment and mouse models and talk science," Lo said. "But the neighborhood design is also prohibitive because each one is locked. You can't just pass by someone else's bench if they are in a different neighborhood. The large foyer is supposed to help, but the only people who actually use it are salespeople. It's mostly just wasted space."

On the other hand, she continued, there's "no space" for administrative or secretarial support staff. "You have to carve out a little area for that from your lab space.

"And the seminar rooms are less than optimal," she added—many are composed of two halves separated by a movable partition, each half owned and shared by a different set of institutes. "If both sides are used at the same time, it's extremely noisy, as there is no sound barrier. And some institutes have converted their side to office space, so there's always hubbub."

Overall, though, she says, she likes the building, its attractiveness, its design. "You know," she sums up, "every building has problems."

—Fran Pollner

Moving On: New Policy Formulated

Asked whether there were any lessons to be learned in solving problems that arose in Building 50, project officer Frank Kutlak noted that there were "many different reasons for some of the shortcomings. . . . Suffice it to say that the experience of occupying Building 50 led to the establishment of a much more formalized planned occupancy policy that was written and issued by ORS and the DCAB [Design Construction and Alteration Branch] that clearly establishes the requirements of both DCAB and the Institutes moving into a building prior to the actual moves."

The "Occupancy Policy for New or Renovated Laboratory Space on the NIH Campus" includes requirements for completion and securing sign-offs from the involved Institutes prior to implementing a move. It can be found by going to

<http://www.nih.gov/od/ors/spacemanage.htm>

and clicking onto "New or Renovated Lab Occupancy Policy." ■

RECENTLY TENURED

Luigi Ferrucci received his M.D. and Ph.D. in biology and the pathophysiology of aging at the University of Florence, Italy, in 1980 and 1983, respectively. He completed his training in geriatric medicine in 1984 and started working at the Italian National Institute on Aging, where he established a continuous collaboration with the NIA Laboratory of Epidemiology, Demography, and Biometry. During the past 15 years, he has spent an average of three months a year at NIA as a visiting scientist. In September 2002 he joined the NIA Clinical Research Branch and is now the Director of the Baltimore Longitudinal Study on Aging.



Luigi Ferrucci

I have always been interested in older people and in aging as a biological process. Only through understanding the multifaceted secrets of aging may we be able to meet the challenges that the demographic transition is posing to the stability of the health-care system in industrialized and developing countries.

My primary research activity focuses on risk factors for physical and cognitive disability in older people, and on the interactive role played by chronological aging, multiple morbidity, and frailty in the disablement process. From my experience as a geriatrician, I am particularly interested in disability that develops progressively and is not explained by any acute event or progressive disease that can be clinically detected.

Scientific questions concerning this type of disablement can only be explored in longitudinal studies with follow-up visits repeated over an extended period of time.

In particular, we are interested in studying subjects with an accelerated decline of muscle mass and strength, changes in body composition, and loss of weight and appetite—a combination of symptoms called the “frailty syndrome.” My current work is aimed at understanding the main causes of frailty in older persons in the attempt to find strategies that can be used to reduce disability in the elderly and to prolong active life expectancy.

I have approached the frailty syndrome from different perspectives. Particularly promising is the study of in-

flammation and its effect on the anatomical integrity and functionality of the different physiological systems. Another puzzling aspect is the ability of humans to compensate for the effect of physical impairments. Compensation may develop at many levels, from specific metabolic pathways to changes in behavior. Understanding compensation may reveal new strategies for delaying and preventing disability in older persons.

I am convinced that good science develops from collaboration and discussion, and I invite scientists at NIH with an interest in the field of aging to contact me. (For a summary of the work of the Baltimore Longitudinal Study on Aging, see BLSA box, page 13.)

Eliot Gardner received his undergraduate training at Harvard University in Cambridge, Mass., where he was introduced to psychopharmacology working directly under the mentorship of two of the field's pioneers, Gerald Klerman and Alberto DiMascio. He received his Ph.D.

in neuroscience and physiological psychology from McGill University in Montreal, Quebec, in 1966 and served as a medical research officer in the U.S. Air Force at the Aeromedical Research Laboratories (U.S. Air Force School of Aerospace Medicine) at White Sands, N.M. He did postdoctoral work in neurology and pharmacology at Albert Einstein College of Medicine in New York City and joined the faculty there in 1972, rising in rank to professor of psychiatry and behavioral sciences, professor of neuroscience, director of basic research in psychiatry, director (and founder) of the Research Residency Training Program in Psychiatry, and co-director (and co-founder) of the Addiction Medicine Fellowship Program. In 2000, he joined NIDA's Intramural Research Program as a senior investigator.

My interests are in the area of the brain mechanisms of reward and reinforcement and their relation to drug addiction. Early in my career, I was one of the first to map the neuroanatomy of reward circuits in the nonhuman primate

brain, and one of the first to suggest that dopamine was the crucial reward-related neurotransmitter in the meso-accumbens reward circuit. I was also one of the first to demonstrate that deep temporal lobe structures, such as the hippocampus and amygdala, modulate reward functions within the meso-accumbens reward circuit.

About 15 years ago, I turned my attention to the psychoactive and addictive constituent of marijuana and hashish: Δ^9 -tetrahydrocannabinol (THC). At the time, THC was considered an “anomalous” addictive substance that did not derive its addictive potential from interaction with the brain's reward circuitry.

In a lengthy series of studies, my lab demonstrated that THC is not anomalous at all, but interacts with the brain's reward circuits in a manner strikingly similar to that of other addictive drugs (*Pharmacol Biochem Behav* 40:571–580, 1991; *Neurobiol Dis* 5:502–533, 1998).

In the course of our work with THC, we also demonstrated clear genetic differences in vulnerability to the rewarding effects of addictive drugs. My work with THC and other cannabinoids continues. (*Chem Phys Lipids* 121:267–290, 2002).

For quite some time, my work on brain reward mechanisms has had a strong medication discovery and development theme (*Am J Addict* 9:285–313, 2000). I believe that our understanding of the neurobiological substrates of addiction has reached a point such that the quest for anti-

addiction medications is now reasonable.

My anti-addiction discovery and development work currently focuses on several neurobiological and psychopharmacological strategies: 1) slow-onset, long-acting inhibitors of the dopamine transporter (DAT), specifically acting within the nucleus accumbens; 2) slow-onset, long-acting enhancers of the neurotransmitter γ -aminobutyric acid (GABA), specifically acting via the GABA-B receptor; and 3) antagonists of the dopamine D3 receptor.

Working with drug-design chemists, my lab has examined a variety of slow-onset, long-acting DAT inhibitors (*J Med Chem* 43:4981–4992, 2000). We find that



Fran Pollner

Eliot Gardner

RECENTLY TENURED

several have promising in vivo profiles in animal model systems—elevating nucleus accumbens dopamine (DA) as assessed by in vivo brain microdialysis, lowering electrical brain-stimulation reward thresholds, and dose-dependently inhibiting intravenous cocaine self-administration.

Working with colleagues at the Brookhaven National Laboratory, we have shown that γ -vinyl-GABA, an irreversible inhibitor of GABA-transaminase, dose-dependently blocks the effects of cocaine, nicotine, heroin, and several other addictive drugs on nucleus accumbens DA as assessed by in vivo brain microdialysis.

It also blocks the effects of cocaine on electrical brain-stimulation reward thresholds, inhibits intravenous cocaine self-administration, dose-dependently blocks both the acquisition and expression of cocaine- and nicotine-induced conditioned cue preferences, and inhibits the acquisition and expression of cocaine-induced neuronal sensitization, a cellular mechanism believed to underlie certain aspects of the addictive disease process (*Synapse* 30:119–129, 1998; *Synapse* 31:76–86, 1999; *Eur J Pharmacol* 414:205–209, 2001; *Synapse* 41:219–220, 2001; *Synapse* 46:240–250, 2002).

These preclinical profiles are promising as predictors of anti-addiction clinical utility.

Working with colleagues at Saint John's University in New York and the GlaxoSmithKline Psychiatry Centre of Excellence for Drug Discovery in the United Kingdom, we have shown that selective D3 receptor antagonism blocks cocaine's enhancement of electrical brain-stimulation reward, blocks the acquisition and expression of cocaine-induced conditioned cue preferences, and blocks cocaine-triggered reinstatement of cocaine-seeking behavior in an in vivo animal model of drug-taking relapse (*J Neurosci* 22:9595–9603, 2002).

From such preclinical studies, we may be close to finding effective pharmacotherapies for addiction in humans.

Most recently, my students and I have shown that reinstatement of cocaine-seeking behavior in lab animals can be triggered by low-intensity, anatomically precise electrical stimulation of two deep brain loci—the ventral subiculum of the hippocampus and the basolateral complex of the amygdala (*Science* 292:1175–

1178, 2001; *Psychopharmacology* 167:in press, 2003). This result is extremely exciting, as these brain loci are selectively activated during drug craving in humans (as determined by neuroimaging techniques such as positron emission tomography) and as this approach allows us to anatomically map the relapse circuits in the brain for the first time.

Mapping the brain's relapse circuits and determining their neurochemical substrates may permit the design and development of specific anti-craving and anti-relapse medications (*Neurobiology of Mental Illness*, 2nd edition, London: Oxford University Press).

These are exciting days in the field of addiction medicine.

Matthew Longnecker received an M.D. from Dartmouth Medical School in Hanover, N.H., in 1981 and completed a residency in internal medicine at Temple University Hospital in Philadelphia. He earned a Sc.D. in epidemiology from Harvard School of Public Health in 1989 and was an assistant professor of epidemiology at the UCLA School of Public Health in Boston before joining the Epidemiology Branch at NIEHS in 1995. He is now a Senior Investigator.

At NIEHS, my research has focused on the health effects of persistent organic pollutants. Through diet, we all are exposed to small amounts of toxic agents that were either manufactured or created inadvertently. These agents are widely dispersed in the environment and bioaccumulate in the food chain. Among the more widely known persistent organic pollutants are dioxins, polychlorinated biphenyls, and dichlorodiphenyl-dichloroethylene, or DDE, a metabolite of the insecticide DDT.

At higher levels of exposure, dioxin is known to be a human carcinogen, and it causes an acnelike skin condition, chloracne. Children who were inadvertently exposed before birth to large doses of a mixture of dioxinlike compounds and polychlorinated biphenyls have several abnormalities, including a persistent deficit on cognitive examinations.

Studies show that poisonings with DDT have temporary neurologic effects, but they do not establish long-term toxic effects, although links with selected cancers have been suggested. The questions that I have addressed focus on potential effects of lower levels of exposure experienced by the general population or—in the case of DDT—by populations exposed to moderate-to-high levels resulting from use in controlling disease vectors (such as mosquitoes).

My interest in the health effects of persistent organic pollutants began with a study of breast cancer in the early 1990s, when cancer epidemiologists devoted much attention to this issue.

When I moved to NIEHS, I wrote a comprehensive review of human data on health effects of persistent organic pollutants. From this, I realized that there were many potential health effects other than cancer for which the mechanistic data were much more suggestive of human effects.

For example, in 1995, investigators showed that DDE—the metabolite of DDT that is ubiquitous in human blood—blocks androgen action. Androgen action

is required in the male embryo for normal development of the genitalia. At that time, rates of male birth defects were increasing, yet there were few data to address whether this pollutant might be responsible.

To pursue the hypothesis that in utero androgen blocking would cause male birth defects, I designed a study that simultaneously addressed other questions regarding the health effects of persistent organic pollutants.

Compared with other studies of the health effects of persistent organic pollutants, my study was huge. It has proven to be a valuable resource for investigating a number of relationships—though the findings regarding DDE and male birth defects were inconclusive.

One of the relationships that was clearly apparent in this study, however, was that women with higher levels of DDE in their blood during pregnancy were more likely to deliver preterm babies (before 37 completed weeks of gestation).

If DDT does lead to an increase in pre-



Matthew Longnecker

term births, it would also be expected to increase infant mortality. DDT is still in use in 25 countries today where users believe it has no adverse effects on humans. Thus, new findings about DDT toxicity could have a significant effect on choice of vector control strategies.

I am following up on potential health effects of DDT exposure through ongoing field work in Mexico, where the pesticide has been used for malaria control.

In conjunction with Mauricio Hernandez at Mexico's National Institute of Public Health, we are studying pregnant women and their offspring, examining a number of health outcomes.

Jeffery Miller received his M.D. from Stanford University in 1985 and completed his internal medicine and chief medical residencies at the University of Colorado at Denver. In 1991, he joined the Molecular Biology Section of the Clinical Hematology Branch of NHLBI and received further laboratory and clinical training in the subspecialty of hematology before beginning his tenure track in the Laboratory of Chemical Biology of NIDDK in 1995. He is now a senior investigator in the Laboratory of Chemical Biology.

My interests are broadly aimed toward the advancement of basic and clinical knowledge involving erythroid cells. Erythroid diseases affect millions of people worldwide and include all forms of anemia, malaria, and hemoglobinopathies.

One of the most fascinating aspects of some hemoglobin-related disorders is that they become clinically important only after birth, when erythroid cells undergo a developmental switch in hemoglobin production from fetal to adult forms.

For this reason, I have pursued several routes toward the clinical goal of increasing fetal hemoglobin in erythroid cells to prevent or treat sickle cell diseases and beta thalassemias, which result from abnormal adult forms of hemoglobin.

My group has focused on understanding the expression of fetal hemoglobin using genome-based information. We began by obtaining highly purified

populations of primary human erythroblasts at defined stages of development and maturation. These cells were used to create gene libraries and a comprehensive database of gene activity.

To date, we have entered into public databases more than 14,000 expressed sequence tags from these libraries. Our eventual goal is the complete description of gene activity associated with the development of erythroid cells. We will make the erythroid genome widely available to the scientific community through the Internet.

On the basis of our profiles of erythroid gene activity, we were able to define the pattern of fetal globin expression as stem cells commit to erythroid development and subsequently accumulate hemoglobin. We determined that fetal and adult genes are expressed with similar patterns during erythropoiesis, albeit at quite different levels, and we are attempting to develop a new model of this process.

In addition, we have determined that signal transduction from growth-related cytokines may be useful for increasing the expression of fetal hemoglobin—even among fully committed populations of adult erythroid cells. We are now using the gene profiles to explore novel signaling networks in erythroblasts in the context of fetal hemoglobin expression.

We hope that this genomic approach will lead to the development of fundamentally new therapies aimed at increasing postnatal production of fetal hemoglobin.

In addition to hemoglobin-related projects, we have applied this genomic approach to the identification of genes encoding novel growth-related or membrane-localized molecules. One project involved the search for the Dombrock blood group carrier molecule. Dombrock is one of the primary antigen groups associated with hemolysis after blood transfusion, but the identity of the Dombrock molecule itself had remained a mystery for more than 35 years.

By mapping the genomic location of the erythroid transcripts in our database, we were able to identify the gene encoding the Dombrock carrier molecule.



Fran Pollner

Jeffery Miller

This knowledge led us to define the single nucleotide polymorphisms responsible for Dombrock-related hemolysis. Through collaboration, we then used this information to develop a molecular assay designed to match donor and recipient blood to prevent hemolysis.

In the future, we plan to continue to use genome-based studies to advance the understanding of basic biological themes manifest during erythropoiesis. We hope this approach will permit us and others to improve the clinical outlook for patients afflicted with erythroid diseases. ■

BLSA To Reassess Assessment Protocols

The Baltimore Longitudinal Study of Aging (BLSA) is the NIA's largest clinical research program and a centerpiece for its studies of human aging. BLSA was launched in Baltimore in 1958, and since then has followed 3,002 participants through a total of 18,432 follow-up visits.

Healthy volunteers, of any age above 20, are recruited for the BLSA and then followed indefinitely through a series of evaluations of their health and aging.

In 2002, 582 subject completed tests of their physiology, biochemistry, psychology, nutrition, sociology, body composition, and health status. A consortium of scientists collects and analyzes the data from the study population, with the aim of characterizing normal and pathological aging.

The basic structure and goals of the BLSA will remain the same, but during the next year, BLSA will be making several important changes in assessment protocols and in the tests performed in the BLSA population.

This transition means that this is an excellent time for potential collaborators with good ideas to contact BLSA chief Luigi Ferrucci (see Recently Tenured profile, page 11) or another BLSA investigator. For info, see

<<http://www.grc.nia.nih.gov/branches/blsa/blsa.htm>>.

DEMYSTIFYING CLINICAL MEDICINE FOR PH.D. SCIENTISTS—AGAIN

Beginning January 7 and continuing to May 27, a weekly course on "Demystifying Medicine," primarily for Ph.D. students, will once again be offered. Postdoctoral fellows, staff physicians, and other students are also welcome to participate.

Building on the success of last year's course, the goal is to aid in bridging the ever-increasing gap between ad-

vances in basic science and their application to human disease. The course is designed to demystify medicine for basic scientists through clinical presentations of patients, pathology, and relevant diagnostic and therapeutic advances linked to advances in basic biology.



Win Arias

There is no fee; however, registration is requested to avoid overcrowding. All sessions are held from 4:00–6:00 p.m. on either Tuesday or Thursday in the ground-floor auditorium of Building 50. For registration and further information, contact [<iarias@helix.nih.gov>](mailto:iarias@helix.nih.gov).

Class Schedule (<http://www1.od.nih.gov/oir/DemystifyingMed/index.html>)

Tuesday, January 7. Hepatitis C: virus and infection (Harvey Alter and Jake Liang)

Tuesday, January 14. HIV: virus and infection (Cliff Lane and John Coffin)

Thursday, January 23. Hospital-acquired infections: mechanisms and vaccines (David Henderson and John Robbins)

Thursday, January 30. Hepatocellular carcinoma: disease and mechanisms (Win Arias and Curtis Harris)

Tuesday, February 4. Multiple sclerosis and other demyelinating diseases (Henry McFarland and colleagues)

Thursday, February 13. Parkinson's disease (John Hardy and Mark Hallett)

Thursday, February 20. Aging:

the process and mechanisms (Richard Hodes and J. Frederick Dice [Tufts])

Thursday, February 27. Atherosclerotic heart disease; cardiovascular imaging: advances (Bob Balaban and Andrew Arai)

Tuesday, March 4. Atherosclerotic heart diseases: mechanisms (Toren Finkel and Julio Chalela)

Tuesday, March 11. Cell transplantation: diabetes mellitus (David Harlan and Ronald Schwartz)

Thursday, March 20. Diabetes mellitus: stem cells and degenerative disease (Phil Gorden and Ron McKay)

Tuesday, March 25. Inflammatory bowel disease: mechanisms (Warren Strober and colleagues)

Tuesday, April 1. Space, Mars and bones (Jay Shapiro [NASA, USUHS] and Pamela Robey)

Tuesday, April 8. Lysosomes: biology and diseases (Juan Bonifacino and Bill

Gahl)

Thursday, April 17. ABC transporter diseases and intracellular trafficking (Jennifer Lippincott-Schwartz and Win Arias)

Tuesday, April 22. Multidrug resistance in cancer (Michael Gottesman and Susan Bates)

Tuesday, April 29. Immunotherapy in cancer (Steven Rosenberg and Pierre Henkart)

Tuesday, May 6. Lymphoma: diseases and advances (Louis Staudt and Lyuba Varticovski)

Tuesday, May 13. Prostatic cancer (Marston Linehan and colleagues)

Thursday, May 22. Predicting disease: molecular advances (Lance Liotta and Francis Collins)

Tuesday, May 27. Finale: futures in biomedical research for PhDs (To be announced)

PERFORMANCE ASSESSMENT AT NIH: NEW RESULTS-ORIENTED CONTRACTS

NIH is implementing a new performance management program that will replace the old performance "plans" with Performance Contracts. These contracts are one aspect of a new, results-focused corporate ("One-HHS") approach to performance management.

Covered Employees

■ All NIH supervisors and managers who are promoted at two-grade intervals—GS-5 to GS-7, GS-7 to GS-9, etc.—will be placed on Performance Contracts. Executives were placed on contracts last year.

System Changes

■ Both the old and new performance management systems use critical elements, BUT the contract approach places greater emphasis on results and measures. **Accountability for performance is key.**

■ Managers at NIH will be asked to examine their mission and targeted outcomes, then determine with more specificity how those outcomes could be achieved.

■ The new contract system focuses on *outputs*, which are very specific, measurable tasks that contribute to achieving outcomes.

■ **All the work performed by all NIH staff** should be derived from broader goals and work performed by their supervisors. The "cascade" effect of activity is a hallmark of the contract approach.

Origins

■ Developed by HHS, this system will be used throughout the Department and has a close relationship to the President's Management Agenda, the Government Performance and Results Act, and other federal initiatives.

Next Steps

■ The Performance Management and Recognition Branch, Division of Employee Relations and Training, NIH Office of Human Resources, will provide "hands-on" briefings to NIH Institutes. Executive officers will be responsible for contract implementation within the Institutes. Stay tuned for updates. ■

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Happy 2003

CALL FOR CATALYTIC REACTIONS

In this issue, we are asking one last back-page question—aptly enough, what might happily go on the back page instead of questions?

Send your suggestions to us via e-mail: [<catalyst@nih.gov>](mailto:catalyst@nih.gov); fax: 402-4303; or mail: Building 2, Room 2W23.

Also, we welcome “letters to the editor” for publication and your reactions to anything on the *Catalyst* pages.

In Future Issues...

- Recruiting Secrets
- A Half-Century
- At the Bedside: CC To Turn 50
- Ethics, Of Course

THIS IS THE LAST QUESTION! Barring cries of outrage from our reading public, we've decided to do away with the back-page questions. We so seldom get answers these days, we decided the space back here could surely be better utilized. So our very last question to you is: any suggestions for what might be put here instead?

YOUR IDEA

COULD GO

HERE

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2W23, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: [<catalyst@nih.gov>](mailto:catalyst@nih.gov)

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